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Thermal Stress

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Abbreviations

AVAs	arterial-venous anastomoses
CNS	central nervous system
EHS	exertional heat stroke
POAH	preoptic area and anterior hypothalamus

Introduction

Thermal stress can have a significant impact on normal physiological functioning if precipitous increases in core temperature are not adequately controlled with behavioral and autonomic mechanisms of body cooling. The United States experiences approximately 200 heat stroke deaths per year with the incidence of heat illness expected to rise as the average life span increases, the rate of obesity is accelerated, and global warming is realized. Heat illness affects all segments of society, although the etiological factors predisposing to heat stroke differ between young adults and the elderly population. The majority of heat illnesses are preventable with improved understanding of the basic thermoregulatory mechanisms of the body's response to heat stress and the development of novel intervention/treatment strategies to mitigate the adverse consequences of this syndrome.

Heat Transfer Mechanisms

The effectiveness of heat transfer mechanisms is critical for the control of core temperature during exposure to extreme environments. Body temperature is normally maintained at a relatively constant level despite nearly continuous heat exchange with the environment. This constancy of core temperature is dependent on a balance between the body's heat exchange with the environment and heat production pathways. Heat transfer between the body and environment occurs by four avenues: conduction, convection, radiation, and evaporation. Radiation, convection, and conduction are effective mechanisms of heat loss but are only effective when skin temperature exceeds that of the environment. Evaporation is the main cooling mechanism used by humans and other mammals when exposed to a hot environment.

Conductive heat transfer occurs when the body surface is in direct contact with a solid object. The degree of conductive heat transfer is directly proportional to the thermal conductivity of the object and skin as well as the amount of surface area in contact with the object. Typically, conduction has minimal effects on core temperature as the contact surface is quite small. Within the body, conductive heat transfer occurs between tissues that are in direct contact with one another, but is limited by the poor conductivity of these tissues. For example, large areas of subcutaneous fat, such as exists in obese individuals, can severely limit conductive heat transfer between the core tissues and the skin and can significantly decrease the effectiveness of conductive cooling during thermal stress. Convection refers to heat transfer between the body surface and external environment as air or water moves over the skin surface. Convective heat transfer may occur as a result of thermal currents, bodily movements, or a combination of the two factors. The wind chill index is an example of the convective cooling effect of wind velocity. Within the body, convective heat transfer occurs between the blood vessels and tissues and is most effective at the capillary beds, which are thin-walled and provide a large surface area for heat exchange. Radiative heat transfer is independent of air movement and occurs as electromagnetic energy is exchanged between the body and surrounding environmental objects. For example, radiative heat gain occurs when the average temperature of surrounding objects (e.g., sky, objects, and ground) is higher than the body surface temperature and is effective even when the air temperature is below that of the body. Evaporation represents a major avenue of heat loss when environmental temperatures are equal to or above skin temperature or when body temperature is increased by vigorous physical activity. In humans, evaporative cooling is achieved as sweat is vaporized, removing heat from the skin surface. In small mammals, such as rodents that are unable to sweat in the heat, evaporative cooling is nonetheless achieved by the grooming of saliva onto the fur and bare skin. The most important environmental variables affecting evaporative cooling in mammals are ambient humidity and wind velocity. In dry air with wind, sweat (or saliva) is rapidly converted to water vapor and readily evaporates from the skin (or fur surface). Conversely, still or moist air limits the conversion of sweat to water vapor. If sweat accumulates and fails to evaporate, sweat secretion is inhibited and the cooling benefit is negated.

Core Temperature Regulation

The control of body temperature in mammals is best described as a two compartmental model consisting of an internal core (i.e., viscera and brain) and an outer shell (i.e., subcutaneous fat and skin). The regulation of a relatively constant internal temperature is critical for normal physiological functioning of tissues and cells, as membrane fluidity, electrical conductance, and enzymes function most efficiently within a narrow temperature range. Most chemical reaction rates vary exponentially with temperature fluctuations, showing a two- to three-fold change in rate for each 10 °C change in body temperature (known as the Q_{10} effect).

Skin temperature is typically more variable than core temperature as it is affected by many facets of the physical environment including temperature, relative humidity, wind velocity, and radiation. Skin blood flow, sweating, and behavioral preferences in humans (insulative clothing, fan cooling) contribute to dynamic changes in skin temperature. Reflexive adjustments in skin blood flow and sweating are used as important mechanisms of temperature control during heat stress. Since the shell represents the final barrier between the core and the environment, it functions as a conductive pathway for core heat transfer to the environment, while also serving as the primary site for sensing changes in environmental temperature. There are a number of nerve endings under the skin (and within the spinal cord and other anatomical sites) that are extremely sensitive to temperature. These warm- and cold-sensitive nerve endings function as receptors and alter their firing rate following an increase or decrease in temperature, respectively. The transmission of nerve impulses from these receptors to the central temperature controlling centers, which reside primarily in the preoptic area and anterior hypothalamus (POAH), provides rapid information regarding changes in skin temperature. These nerve impulses impinge on thermal-sensitive neurons within the POAH that integrate the information and activate autonomic and behavioral heat transfer mechanisms to counterbalance the initial temperature perturbation and maintain core temperature at a homeostatic level (**Figure 1**).

In humans, core temperature can be measured at several anatomical sites, but caution is warranted as oral, tympanic, esophageal, and rectal temperature measurements often differ from one another. The most important factor to consider with core temperature measurements is the ability to insulate the measurement device from the influence of environmental and surface temperature. Oral temperature is considered similar to blood temperature due to the rich blood supply of the tongue, but may misrepresent core temperature if the patient is cooling the mouth by hyperventilating, as often occurs during heat illness. Tympanic temperature is considered a sensitive measure of core temperature as it responds more rapidly to cooling or heating than rectal temperature. However, tympanic temperature can be influenced by environmental temperature as it is responsive to changes in skin temperature of the head and neck. It is recommended during tympanic temperature measurements that the ear is insulated from the environment using the palm of the subject's hand to prevent cool ambient temperatures (<30 °C) from impacting this measurement, but this precaution is often overlooked. Esophageal temperature is the most accurate and responsive to changes in blood temperature, although instrumentation may not be feasible in severely injured, unresponsive patients. Rectal temperature has a slower response rate and gives slightly higher readings than other sites in the core, including esophageal temperature. However, rectal temperature is considered a highly reliable indicator of core temperature.

Although normal core temperature in humans is reported as 98.6 °F (37 °C), regional variability is observed and depends on factors such as tissue metabolic activity, local blood supply, and temperature gradients between neighboring tissues. There is also considerable variability between individuals ($\leqslant 1$ °C) due to innate biological variability and normal fluctuations throughout the circadian cycle. The circadian core temperature variation in humans is well characterized with low temperature readings of ~ 36.1 °C in the early morning on waking, a steady rise during the day with a peak at ~ 37.2 °C and low temperatures during the night (nadir from 2 a.m. to 4 a.m.). Conversely, nocturnal mammals such as rodents show a circadian rhythmicity that is opposite to that of humans, with low daytime (~ 36 °C) and high nighttime (~ 38 °C) values. Although circadian rhythmicity appears to be correlated with activity patterns, with high activity during the day inducing rises in core temperature, shift workers who are active during the night and sleep during the day do not show a reversal of their core temperature profiles. However, acute exercise bouts can have profound effects on core temperature regulation. In humans at rest, $\sim 70\%$ of metabolic heat is generated by the viscera/internal organs of the body, whereas during exercise skeletal muscle may account for up to 90% of total metabolic heat. The temperature of active skeletal muscle will differ dramatically from other areas of the body that are not directly involved in the activity meaning that core temperature measurements will differ during exercise depending on the site of measurement.

Mechanisms of Heat Dissipation during Thermal Stress

Peripheral vasomotor tone is a critical, first responding mechanism to dissipate excess body heat during thermal

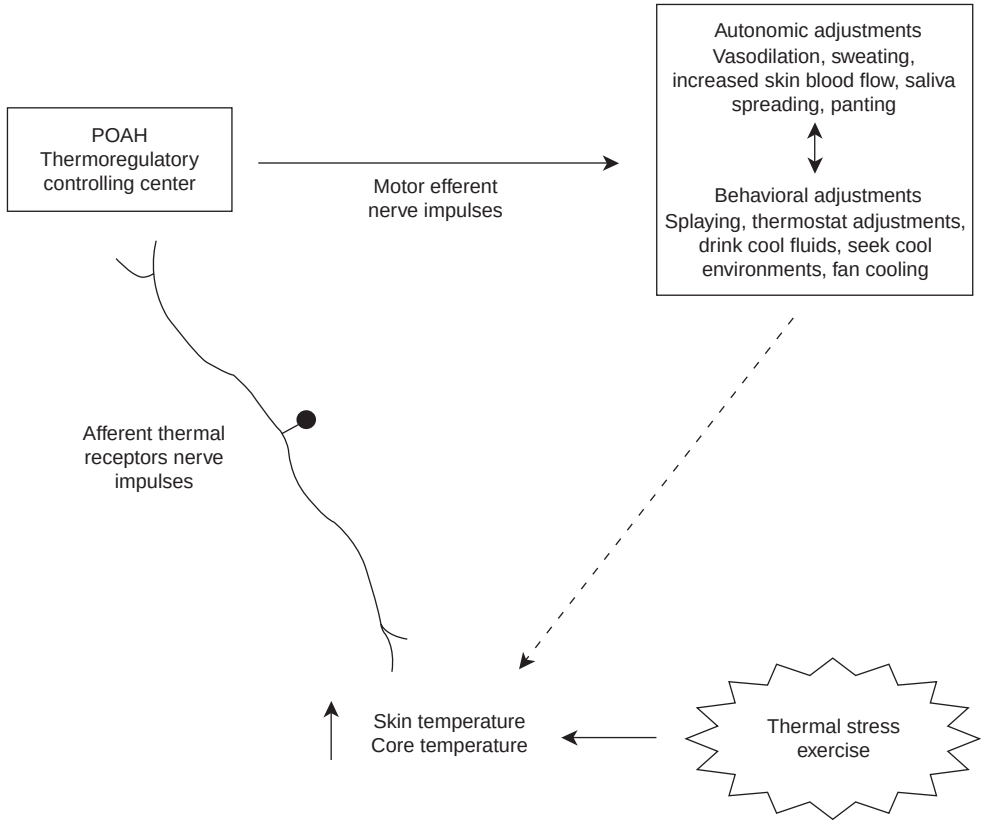

Figure 1 Negative feedback pathway regulating core temperature in humans and other homeotherms. Warm- and cold-sensitive thermal receptors located in the skin, spinal cord, and other anatomical sites sense changes in temperature that alter skin or core temperature. Nerve impulses from these receptors are relayed to the thermoregulatory controlling center within the preoptic anterior hypothalamus (POAH). The POAH acts as a thermoregulatory integration center, comparing sensory temperature information to a set point temperature and responds with corrective motor outputs involving autonomic and behavioral responses, which typically act in conjunction with one another to maintain a normal core temperature. Under prolonged thermal stress, these effector responses may become fatigued, resulting in precipitous elevations in core temperature that can culminate in heat stroke, multiorgan system failure, and death. ——▶ indicates stimulatory pathway, - - - - - - - - ▶ indicates inhibitor pathway.

stress. Cardiovascular mechanisms have evolved to shunt warm blood from the body core to the periphery to increase heat loss by radiation and convection while preserving normal control of blood pressure. Mean skin blood flow can vary by ~10-fold in humans depending on the thermal environment. The most effective anatomical location for alterations in skin blood flow to affect dry heat loss is in the hands and feet, which are concentrated with arterial-venous anastomoses (AVAs). During heat exposure, the AVAs serve as important avenues for heat loss as they shunt large volumes of blood to the skin for heat dissipation. Similar mechanisms exist to facilitate dry heat loss in small rodents, as nonfurred surfaces, such as the ears and tail, have a high surface area to volume ratio and an abundance of AVAs to facilitate convective heat transfer. Under conditions of severe or prolonged heat stress, increased blood flow to the skin surface occurs concomitantly with sweat secretion. The density, secretion rate, and activation threshold of regional sweat glands are the determining factors for the volume of sweat loss experienced at any particular body site. In general, the back and chest show the highest sweating rates for a given core temperature in humans. Fluid losses from excessive sweating may be as high as 2 l per hour under conditions of prolonged heat exposure, which if not adequately replenished, can induce significant dehydration. The respiratory surfaces represent an important avenue for evaporative and dry heat loss as well. Panting is an effective method of evaporative heat dissipation in large animals such as birds, dog, sheep, and rabbits and is performed at a resonant ventilation frequency that requires minimal energy expenditure. Nonpanting homeotherms, such as humans and rodents, show an increase in breathing frequency and minute volume during severe heat exposure, which facilitates evaporative cooling from the respiratory surfaces, but is not representative of panting per se. Owing to its larger surface area, the skin surface is a more effective avenue than the respiratory surfaces for environmental heat exchange.

When available and effective, behavioral thermoregulation is the preferred method of heat transfer in mammals, as it involves minimal metabolic energy expenditure. Behavioral mechanisms are utilized by all mammals for homeostatic temperature control, including humans. Examples of behavioral mechanisms of heat loss in humans include the removal of clothing (increased exposure of the skin surface to the environment), thermostat adjustments, consumption of cool fluids, and the use of a fan or air conditioner for cooling (convective heat transfer). Under normal conditions, autonomic and behavioral thermoregulatory mechanisms function in concert with one another to maintain thermal balance for homeostatic control and in response to thermal extremes. However, the suppression of behavioral mechanisms of temperature control may occur during sleep, illness, trauma, or severe thermal stress. Autonomic heat transfer mechanisms can also become exhausted under conditions of prolonged stress. For example, during heat exposure, the sweating mechanisms may become fatigued if adequate hydration is not maintained and an individual becomes extremely dehydrated. This can lead to a precipitous rise in core temperature resulting in heat illness and tissue injury.

The Heat Illness Continuum

Heat illness is a complicated clinical condition to prevent and treat because individuals vary widely in their susceptibility and there remains a limited understanding of the mechanisms that are responsible for multiorgan system failure and death. Heat stroke is the most widely recognized condition of the heat illness continuum, as it receives considerable recognition in the popular press following deaths during yearly heat waves throughout the world. However, heat illness is best thought of as a continuum that ranges from heat cramps, which are fairly innocuous to the moderate illness of heat exhaustion and culmination in the life-threatening condition of heat stroke.

Heat cramps occur following strenuous work and profuse sweating. Spasms of skeletal muscles in the extremities may be sporadic, but painful and typically develop in individuals unacclimatized to physical exertion. Interestingly, heat cramps also occur in well-conditioned athletes who experience an excessive loss of electrolytes. Heat cramps typically occur following exercise in the cold when environmental temperature does not exceed core temperature. The highest incidence of cramps occurs in the skeletal muscles involved in the physical activity. Current treatment strategies for heat cramps include resting in a cool environment and replacement of electrolytes (potassium, sodium) and fluid volume. Although prevention strategies against heat cramps include the salting of food and fluid ingestion before the activity, the use of salt tablets is not warranted as it may cause gastrointestinal irritation.

Heat exhaustion (also referred to as heat prostration or heat collapse) is the most common heat illness syndrome, resulting from water or salt depletion in a hot environment. In severe instances of heat exhaustion, there is an inability to maintain adequate cardiac output, resulting in an elevation in core temperature and the potential for collapse. Heat exhaustion is often observed in the elderly as a result of combined use of medications (e.g., diuretics), lack of adequate water intake, and preexisting cardiovascular insufficiency. There are multiple symptoms associated with heat exhaustion including nausea, dizziness, headache, confusion, agitation, loss of appetite, weakness, fatigue, and thirst. Clinical signs of heat exhaustion include cold clammy skin, pale complexion, dilated pupils, an elevated pulse rate, and orthostatic hypotension. The main clinical treatment is to place the patient in a recumbent position in a cool environment to facilitate cooling and the return of normal blood pressure. Oral fluid ingestion with electrolytes may be adequate for recovery, although IV fluid administration is often warranted in severely dehydrated individuals.

Heat stroke is a life-threatening condition that is clinically characterized by elevated core temperature (typically, but not always $>40\,^{\circ}C$), hot dry flushed skin, and central nervous system (CNS) dysfunction. The use of a specific core temperature for clinical evaluation can be misleading as patients vary widely depending on the length of heat exposure, time of clinical admission following collapse, and several other factors. Clinical symptoms of heat stroke vary widely depending on the degree of temperature elevation, but include headache, fainting, seizures, confusion, vertigo, hallucinations, delirium, and possibly coma. Hemoconcentration and electrolyte distrubances are clinical indices of heat stroke that can be ameliorated with proper fluid and electrolyte ingestion before or during physical exertion in a hot environment. Although removal from the heat and rapid cooling is essential for heat stroke survival, a variety of complications ensuing after heat exposure make the choice of treatment modalities difficult. The outcome from individuals who develop the clinical definition of heat stroke is dismal with ~ 200 deaths per year. Up to 30% of heat stroke survivors experience permanent neurological impairments or death within 1 year of hospitalization.

One of the main reasons for the lack of development of effective clinical prevention or treatment therapies for heat stroke is the complicated nature of the syndrome, as there are different classifications of heat stroke that differ in their etiology and physiological mechanisms of injury. Classic (or passive) heat stroke occurs in nonexercising

Table 1 Medications that predispose to heat stroke

Medication	*Effect*
Diuretics	Salt, potassium and calcium depletion; dehydration
Anticholinergics (atropine)	Reduced sweating
β-Blockers (propranolol)	Reduced blood pressure; reduced skin blood flow
Antihistamines	Reduced sweating
Stimulants (ephedrine)	Heat production
Antidepressants	Heat production, agitation, and reduced sweating

Table 2 Thermoregulatory deficits with aging

Reduced peripheral vasoconstriction
Attenuated increase in cardiac output
Attenuated redistribution of renal and gut circulation
Smaller sweat gland output
Structural skin alterations that inhibit skin blood flow responses

individuals who are immunocompromised before heat exposure, whether due to aging or a preexisting medical condition, such as mental illness, alcoholism, atherosclerosis, hypertension, or drug use (e.g., diuretics and anticholinergics) (Table 1).

Cardiac insufficiency limits the ability to shunt core blood to the skin surface for effective heat transfer and prevents the maintenance of adequate cardiac output, which is a predisposing factor for circulatory collapse. Alcohol can impede vasomotor reflexes during heat exposure while stimulating metabolism, resulting in an increase in heat production. The elderly are particularly susceptible to classic heat stroke and represent the population sector that experiences the highest mortality rates during summer heat waves. In addition to their higher use of medications, the elderly may develop thermoregulatory deficits that impair heat loss mechanisms (Table 2).

A second type of heat stroke condition that is not as widely recognized, but occurs in young, health individuals undergoing strenuous physical activity is referred to as exertional heat stroke (EHS). EHS presents as a different clinical picture than classic heat stroke due to the direct effects of strenuous exercise on physiological responses, which are difficult if not impossible to dissociate from the effects of heat stress alone. The symptoms of EHS include an unsteady gait, dizziness, sweaty skin surface, tachycardia, headache, nausea, cramps, ataxia, and confusion. A long-term consequence of EHS is an exaggerated systemic inflammatory response that ensues following muscle or heat injury and is associated with coagulopathies (disseminated intravascular coagulation, hemorrhage), fever, cell death, and multiorgan system failure.

Table 3 Heat stroke circulatory and tissue abnormalities

Circulatory
Hemoconcentration
Hyperkalemia
Hypocalcemia
Hypernatremia
Elevated muscle enzymes (CK)
Elevated liver enzymes (AST, ALT)
Coagulopathies (DIC)
Hyperglycemia or hypoglycemia
Increased cytokines
Lactic acidosis
Tissue
Rhabdomyolysis
Myoglobinuria
Cardiac failure with tachycardia
Jaundice
Acute oliguric renal failure

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; DIC, disseminated intravascular coagulation.

Kidney and liver damage are also common. Renal failure may occur due to high protein concentrations occurring with rhabdomyolysis or myoglobinuria. Urinalysis often reveals proteinuria in the presence of red blood cells (Table 3).

Heat stroke Risk Factors

Heat stroke risk factors include a lack of heat acclimatization, poor fitness level, prior illness, obesity (high body fat mass), geographical region of origin, dehydration, and the use of certain medications. Individuals from southern climates may be less susceptible to heat stroke than those from northern climates, due to adaptive changes to heat exposure that southern residents accumulated within their lifetime. The wearing of protective clothing is a significant predisposing factor to EHS in athletes (heavy uniforms), military personnel, (chemical protective clothing), or during occupational activities (e.g., pesticide workers, firefighters, and race car drivers). Normal clothing has sufficient ventilation allowing for effective heat loss by convection and evaporation in relatively warm environments. However, protective clothing can consist of multiple layers and often encapsulates the head (a site of significant heat exchange). An insulative layer of air between the skin and the environment is formed with protective clothing that impedes convective and evaporative heat exchange. Although this can be uncomfortable in a room temperature environment, the protective clothing can quickly result in a dangerous elevation in core temperature when worn in a warm environment.

Social factors predisposing elderly individuals to classic heat stroke include living alone, an inability or unwillingness to leave one's home, residing on the top

floor of buildings (heat rises), and socioeconomic status. Inhabitants of urban dwellings are exposed to greater intensity and longer duration of heat exposure because concrete structures do not effectively dissipate heat as the environmental temperature decreases during the nighttime. The use of air conditioning units is an effective method to facilitate convective cooling, but this may be limited or unavailable in individuals of low socioeconomic status. The unwillingness of the elderly to leave their residences and the presence of high indoor temperatures in the absence of air conditioning units (or refusal to use those units) magnify the intensity and duration of heat stress. The high death toll ($\sim$15 000) in the 2003 France heat wave is partly explained by culture, as air conditioning units are not prevalent in residences, retirement homes, or hospitals in that country. This factor in combination with the large population of people $\geq$100 years old ($\sim$10 000) was a predisposing factor for the high death toll experienced in that country in the 2003 heat wave.

Prevention and Treatment Strategies

Cooling therapy is currently the most effective heat stroke treatment. Heat stroke victims should have their clothing immediately removed and rapidly cooled to a core temperature below 38.8 °C, which is essential for the prevention of injury and death. Cooling can be achieved by several methods, including immersion in ice water, covering with cold, wet blankets, or packing the body with ice packs. Fan cooling should be used to accelerate convective heat loss and skin massage is effective to stimulate return of cooled peripheral blood to the viscera and brain. Unfortunately, heat stroke victims who are ill, poor, or elderly are often discovered several hours or days following heat exposure, and they have a much poorer outcome, despite cooling therapy.

Most heat waves occur across 3 or more days with the majority of hospitalizations and deaths occurring within 24 h of the onset of the event. The majority of heat stroke deaths occur during the initial days of a heat wave as individuals are unacclimatized to elevated temperatures. The incidence of EHS in the summer can be minimized by scheduling athletic events during the early morning or evening hours when temperature and humidity are typically lower. The enforcement of adequate fluid hydration and avoidance of alcohol can minimize dehydration before a scheduled athletic event. Heat acclimatization is an effective method to decrease heat stroke susceptibility during annual heat waves and can be achieved following repeated exposure (typically 7–10 days) to elevated environmental temperatures, exercise, or the combination of those two factors. Several aspects of the sweating response are improved in heat acclimatized individuals including a more profuse and rapid sweating response (starts at a lower core temperature) and redistribution of sweat to the limbs, which improves evaporative cooling as it takes advantage of the large surface area of the extremities for heat dissipation. Acclimatized individuals secrete a more dilute sweat due to increased secretion of the mineralcorticoid hormone aldosterone, which stimulates sodium reabsorption during sweat production. However, heat acclimatization effects will dissipate fairly rapidly if continued exposure to the stressor does not occur. The benefits can also be reduced if the individual suffers an illness, consumes copious amounts of alcohol, or is dehydrated.

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